chromosomal level or at a gene expression level. These may include inactivation of tumor suppressor genes, activation of oncogenes or specific translocations at the chromosomal level. Some genetic changes at the chromosomal level and gene expression level have been well documented for other brain tumors (Furnari *et al.,* 1995, Cancer Surv., 25:233-275). For example, it has been documented that loss of tumor suppressor(s) genes at chromosome 10, mutations in p53, or overexpression of epidermal growth factor receptor, may be major events leading to glioblastoma multiforme. A number of other genes such as EGFR, CD44, β4 integrins, membrane-type metalloproteinase (MT-MMP), p21, p16, p15, myc, and VEGF have been shown to be overexpressed in different types of brain tumors (Faillot *et al.,* 1996, Neurosurgery, 39:478-483; Eibl *et al.,* 1995, J. Neurooncol., 26:165-170; Previtali *et al.,* 1996, Neuropathol. Exp. Neurol. 55:456-465; Yamamoto *et al.,* 1996, Cancer Res., 56:384-392; Jung *et al.,* 1995, Oncogene, 11:2021-2028; Tsuzuki *et al.,* 1996, Cancer, 78:287-293; Chen *et al.,* 1995, Nature Med., 1:638-643; Takano, *et al.,* 1996, Cancer Res., 56:2185-2190; Bogler *et al.,* 1995, Glia, 15:308-327). Several cell adhesion molecules (CAMs), such as integrins, cadherins, IgSF proteins (carcinoembryonic antigen, N-CAM and VCAM-1) or lectins, are thought to be involved in tumorigenesis (Johnson, 1991, Cancer Metastat. Rev. 10: 11-22). Over-expression of anti-sense to the secreted glycoprotein SPARC (secreted protein, acidic and rich in cysteine), results in suppression of the adhesive and invasive capacities of melanomas (Ledda *et al.,* 1997, Nature (Med). 3: 171-176). The cell-surface adhesion molecule MCAM (MUC18) when over-expressed may lead to increased adhesion and metastatic potential of human melanoma cells in nude mice (Xie *et al.,* 1997, Proc. Nat'l Cancer Conf. 38:522). Expression of N-CAM or ICAM (Intercellular adhesion molecule) is related inversely to increased metastasis (Hortsch, 1996, Neuron 17:587-593). Other genes such as p53 show mutations in the majority of brain tumors (Bogler *et al., supra*). How the interplay of one or more of these genes leads to tumorigenesis is not known but most likely multiple steps are required for neoplastic transformation. The exact series of events that lead to initiation or progression of glioblastoma are not known at present and useful markers for early detection of brain tumors are lacking.

Kindly replace the paragraph beginning at page 6, line 5, with the following substitute paragraph:

DCC is a cell adhesion molecule that belongs to the N-CAM family. DCC was first shown to be expressed in a variety of tumors including the brain and lung but its expression was reduced and mutated in a number of colorectal carcinomas (Fearon, *et al.*, 1990, Cell, 61:759-767). The down-regulation or mutation of the DCC molecule leads to the disruption of normal cell-cell adhesion in the intestinal epithelium. This process is known to play an important role in the metastasis of colorectal carcinomas (Albelda, 1993; Fearon *et al.*, 1990).

B2

Kindly replace the paragraph beginning at page 13, line 22 with the following substitute paragraph:

Figures 2 (A-D) present the nucleotide and amino acid sequences of human Nr-CAM as well as the results of nucleotide sequence analysis as described in Section 6 (Figure 2C) and a schematic illustration of the *hNr-CAM* gene showing the area used herein for antisense targeting (Figure 2D). Figure 2A presents the nucleotide sequence of human Nr-CAM (SEQ ID NO: 1). Features of the nucleotide sequence include the following: Nucleotides 130-3615 encode the extracellular domain; nucleotides 202-4026 encode product = hBRAVO-Nr-CAM; nucleotides 316-483 encode the Immunoglobulin I domain; nucleotides 613-768 encode the Immunoglobulin II domain; nucleotides 988-1134 encode the Immunoglobulin III domain; nucleotides 1258-1410 encode the Immunoglobulin IV domain; nucleotides 1540-1719 encode the Immunoglobulin VI domain; nucleotides 2113-2265 encode the first Fibronectin (Fn) repeat; nucleotides 2413-2565, the second Fn repeat; nucleotides 2710-2886, the third Fn repeat; nucleotides 3028-3186 the fourth Fn repeat; nucleotides 3370-3510, the fifth Fn repeat; nucleotides 2616-3684, the transmembrane region; nucleotides 3685-4036, the intracellular domain; and nucleotides 4030-4134 constitute a 3' untranslated region. Figure 2B presents the amino acid sequence of human Nr-CAM (SEQ ID NO: 2). The hydrophobic signal sequence is underlined. Figures 2A and 2B are adapted from Lane *et al.*, 1996, Genomics 35:456-465.

B3

Kindly replace the paragraph beginning at page 14, line 13 with the following substitute paragraph:

B4

Figure 2C illustrates nucleotide sequence identity analysis between previously cloned *hNr-CAM* (Accession Number U55258; SEQ ID NO: 3), *rat Nr-CAM* (Accession Number U81037; SEQ ID NO: 4) and the sequence of clone D4-1 (SEQ ID NO: 5) obtained by cloning the hNr-CAM isolated by DD-PCR into pCRII vector (Invitrogen). Sequence identity analysis was performed using the DNasis program from Hitachi Software (South San Francisco, CA). Stars (*) indicate presence of identical nucleotides among the sequences.

Kindly replace the paragraph beginning at page 20, line 19 with the following substitute paragraph:

B5

Figure 24 shows the sequence identity analysis between human (SEQ ID NO: 31) and rat (SEQ ID NO: 32) *Nr-CAM* nucleotide sequence.

Kindly replace the paragraph beginning at page 36, line 18 with the following substitute paragraph:

B6

The *Nr-CAM* sequences provided by the present invention include those nucleotide sequences encoding substantially the same amino acid sequences as found in native Nr-CAM proteins, and those encoded amino acid sequences with functionally equivalent amino acids, as well as those encoding other Nr-CAM derivatives or analogs, as described in Section 5.2.5 *infra* for Nr-CAM derivatives and analogs.

Kindly replace the paragraph beginning at page 54, line 16 with the following substitute paragraph:

B7

In addition, assays that can be used to detect or measure the ability to inhibit, or alternatively promote, cell proliferation are described herein.

Kindly replace the paragraph beginning at page 63, line 5 with the following substitute paragraph:

The Therapeutics of the invention that antagonize Nr-CAM activity can also be administered to treat or inhibit premalignant conditions and to inhibit or prevent progression to a neoplastic or malignant state, including but not limited to those disorders listed in Table 1. Such prophylactic or therapeutic use is indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W.B. Saunders Co., Philadelphia, pp. 68-79). Hyperplasia is a form of controlled cell proliferation involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. As but one example, endometrial hyperplasia often precedes endometrial cancer. Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplasia can occur in epithelial or connective tissue cells. Atypical metaplasia involves a somewhat disorderly metaplastic epithelium. Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation, and is often found in the cervix, respiratory passages, oral cavity, and gall bladder.

B8

Kindly replace the paragraph beginning at page 72, line 10 with the following substitute paragraph:

B9

Additional methods that can be adapted for use to deliver a nucleic acid encoding a Nr-CAM protein or functional derivative thereof are described herein below.

Kindly replace the paragraph beginning at page 73, line 32 with the following substitute paragraph:

B10

In other embodiments, chemical mutagenesis, or homologous recombination with an insertionally inactivated *Nr-CAM* gene (see Capecchi, 1989, Science 244:1288-1292 and Section 5.14 *infra*) can be carried out to reduce or destroy endogenous Nr-CAM function, in order to decrease cell proliferation. Suitable methods, modes of administration, and compositions ~~,~~ that can be used to inhibit Nr-CAM function are described herein.

Kindly replace the paragraph beginning at page 80, line 27 with the following substitute paragraph:

B11

Additional methods that can be adapted for use to deliver a Nr-CAM antisense nucleic acid are described herein.

Kindly replace the paragraph beginning at page 98, line 4 with the following substitute paragraph:

B12

In this study, the role of Nr-CAM in brain tumorigenesis was characterized.

Kindly replace the paragraph beginning at page 108, line 10 with the following substitute paragraph:

B13

Genomic Southern blot was performed as described in Section 6.1.7 on 3 brain tumor cell lines (astrocytoma III, glioma and glioblastoma) and the NIH3T3 cell line. As show in Figure 9 no change in the genetic level of *hNR-CAM* was observed in the 4 cell lines tested.

Kindly replace the paragraph beginning at page 118, line 6, with the following substitute paragraph:

B14

As shown in Figure 20C, a 17 fold increase in the number of cells undergoing apoptosis was observed. These results clearly suggest that antisense hNr-CAM over-expression caused 5GB glioblastoma cells to become more sensitive to UV radiation.

Kindly replace the paragraph beginning at page 128, line 29 with the following substitute paragraph:

In order to identify genes that are altered by the *hNr-Cam* gene product in 5GB glioblastoma cells, we compared the expression of 5000 genes in pCMV-neo or pCMV-1/3Nr-AS transfected 5GB glioblastoma cells using the Array technique. Two identical Human GeneFilters™ were differentially hybridized with cDNA prepared from pCMV-neo or pCMV-1/3Nr-AS transfected 5GB glioblastoma cells. Two identical array membranes containing 5000 genes were purchased from Research Genetics. The membranes were prehybridized in a pre-hybridization solution for 12 hours. Hybridization was done with a $1x10^5$ cpm/ml cDNA probe. This probe was prepared by carrying out 1st strand synthesis from pCMV-neo or pCMV-1/3Nr-AS transfected 5GB glioblastoma cells 1µg polyA$^+$ mRNA. First strand cDNA synthesis was carried out using the Advantage cDNA synthesis kit from Clontech. The membranes were washed in a wash solution (0.1%SDS/1XSSC) for 30 minutes at room temperature and then at 50°. Membranes were then exposed to X-ray film. Results are presented in Figures 26 (A and B).